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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,181	11/10/1999	Snezna Rogelj	UNME-0054-1	7645

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	23

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/424,181	ROGELJ ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-35* is/are pending in the application.

4a) Of the above claim(s) *9,10,12-20 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) *2-5,8 and 11* is/are allowed.

6)☒ Claim(s) *6,7 and 21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant paper No. 22 (filed 11/19/02), claims 2-8, 11, 21-26, 28-33 have been amended. Claims 2-8, 11, 21-34 are examined in this Office action; claims 9, 10, 12-20, 35 remain withdrawn from consideration.

Applicants' arguments filed 11/19/02 have been considered and found persuasive in part.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-27 and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 28-34 are drawn to a method of treating viral infections such as HIV. As clarified by applicants, figure 3 shows that PAO* [*para*-N-(ethane-2-sulfonic acid)amino phenylarsenoxide] promoted L-selectin shedding from neutrophils. In addition, on page 21, line 19, it is asserted that PAO* exhibited anti-HIV activity in an assay which might have been the same as that described in Weislow (*J Natl Cancer Inst* **81**, 577, 1989), or it may

have been different therefrom. However, no results were presented, and so it is not possible to determine what activity this compound might have exhibited, or even what the assay was. It is also not possible to determine what control experiments might have been carried out. If ostensibly inactive compounds gave a positive result, for example, it would cast doubt on the signficance of whatever result may (or may not) have been obtained for PAO*. In addition, Bennett T. A. (*Journal of Immunology* **164** (8) 4120-9, 2000) discloses that phenylarsine oxide promotes L-selectin shedding from leukocytes. However, it is not established that phenylarsine oxide or any of the claimed compounds actually inhibit PDI. Moreover, there is no evidence from the prior- or post-art that **if** a given compound promotes L-selectin shedding from neutrophils, the compound is an inhibitor of PDI. Accordingly, claims 21-27 are rejected because there is no evidence that PDI is inhibited. However, if it should turn out, at some point in the future, that the claimed compounds actually do inhibit PDI, then perhaps the following claims would become enabled (no determination has been made as to what might or might not constitute new matter):

> *A method of inhibiting entry of HIV (human infectivity virus) into cells comprising contacting said cells with a compound according to claim 2 for a time and under conditions effective to inhibit protein disulfide isomerase.*

> *A method of inhibiting entry of HIV (human infectivity virus) into cells of a human subject comprising administering to a human subject in need thereof a compound according to claim 2 for a time and under conditions effective to inhibit protein disulfide isomerase.*

Or perhaps applicants will be able, at some point in the future, to provide evidence that it is well known in the art that if a compound is effective to promote L-selectin shedding from neutrophils, then it will inhibit entry of HIV into cells. Should such an event come to pass, then perhaps the following claims would become enabled:

> *A method of inhibiting entry of HIV (human infectivity virus) into neutrophils comprising contacting said neutrophils with a compound according to claim 2 for a time and under conditions effective to promote L-selectin shedding from said neutrophils.*
>
> *A method of inhibiting entry of HIV (human infectivity virus) into cells of a human subject comprising administering to a human subject in need thereof a compound according to claim 2 for a time and under conditions effective to promote L-selectin shedding from neutrophils.*

That is, it is applicants who have been enthusiastic advocates of the proposition that **if** a compound is effective to promote L-selectin shedding from neutrophils, **then** it will inhibit entry of HIV into neutrophils (or at least into cells that express CD4). Applicants would also have to concede that if a compound **fails** to promote L-selectin shedding from neutrophils, then either of the following must be true: (a) the compound will fail to inhibit entry of HIV into cells, or (b) if the compound does inhibit entry of HIV into cells, the inhibition will occur irrespective of the presence or absence of PDI. Thus, given applicants convictions on this matter, applicants should feel no reluctance to amend the method claims to recite that the compound is administered *for a time and under conditions*

effective to promote L-selectin shedding from neutrophils.

As indicated above, if it should turn out, at some point in the future, that the claimed compounds actually do inhibit PDI, then perhaps one could expect some inhibition of viral entry into certain types of cells, especially those expressing CD4, to which the envelope glycoprotein gp120 binds. However, even if such inhibition can be made to occur in vitro, or in vivo, it will not follow therefrom that HIV infections in humans can be successfully treated. Each of claims 28-33 encompasses treatment of HIV infections in humans.

The fact is that *in vitro* inhibition of HIV replication is not predictive of an effective therapy in humans. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As stated in Mangos (*Texas Medicine*, **86**, 40, 1990):

> "In spite of ... [therapy against HIV and opportunistic infections], the universal outcome of HIV infection / AIDS is the death of the patients" (see, e.g., abstract).

As disclosed in Binquet (*AIDS* **12**, 2313, 1998) a total of 556 patients were treated with HIV protease inhibitors for a period of 230 days, and that despite being treated with with HIV protease inhibitors for more than seven months, 24 of the patients had died. Both of these references teach that death occurs in spite of administration of HIV protease inhibitors. If

death is the result of a treatment, one cannot say that success (in the treatment) is predictable.

If sucess is not predictable, it must be "unpredictable". Given that treatment of AIDS is "unpredictable", it follows therefrom that "undue experimentation" would be required to determine which, if any, of the claimed compounds can be used to treat patients afflicted with AIDS. [*Ex parte Balzarini,* 21 USPQ2d 1892)]. Thus, extrapolation from *in vitro* inhibition of viral replication in a petri dish to a therapy in humans is unpredictable.

If no further evidence can be obtained by applicants, it is suggested that all pending method claims be cancelled, and replaced by claims which are drawn to a method of promoting L-selectin shedding from neutrophils.

*

Claims 6-7 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 6 recites that the $-SO_3$ group is attached to a ring carbon. However, this is ambiguous, since claim 5 (on which claim 6 is dependent) mandates the presence of two separate aryl rings (one bearing arsenic, the other bearing sulfate). It is suggested that the claim be amended to make clear which of the two aryl rings the sulfonate group is bonded to.

- Claim 7 recites that the $-SO_3$ group is attached to a ring carbon via an alkylene group. However, this constitutes a contradiction. If the SO_3 group is attached to a carbon atom of the aryl ring, then there is a covalent bond between a sulfur atom and a carbon atom, wherein said carbon atom is a aryl ring member atom. It is impossible for an SO_3^- group to be attached to an aryl ring member atom, and at the

same time, to be bonded to an alkylene group. In addition to constituting a contradiction, claim 7 is not properly dependent on claim 6. Claim 6 mandates that one of R and R' is an aryl group that "contains" at least one SO_3 group. However, claim 7 mandates that an alkylene group be present in addition to the aryl group. Thus, claim 7 mandates the presence of an alkylaryl (or arylalkyl) group; as such, the claim dependence is not proper.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 28-34 are rejected under 35 U.S.C. §103 as being unpatentable over Arbault, S. (*Biomedicine and Pharmacotherapy* **51** (10) 430-8, 1997).

Arbault discloses that phenylarsine oxide inhibits HIV replication. Thus it would have been obvious to one of ordinary skill that if HIV replication can be inhibited, an HIV-infected patient can be successfully treated by administering the phenylarsine oxide.

Thus, the claims are rendered obvious.

✺

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton

DAVID LUKTON
PRIMARY EXAMINER
GROUP 1600